

US App. No. 10/517,328
Response to 12/14/07 Office Action

REMARKS

The claimed invention is directed to methods of treating cancers characterized by excessive Rsk activity. Applicants were the first to discover that excessive Rsk activity is associated with various cancers and that the growth of such cancers could be inhibited by the use of a Rsk specific inhibitor. Claims 21 and 25 have been amended to specifically identify cancer types whose growth has been demonstrated by applicants to be significantly inhibited (e.g. 50% growth inhibition by 25 uM or less of the Rsk inhibitor). Support for that amendment is found on page 7, lines 24-31.

Applicants have canceled previously withdrawn claims 10-12, 17-20 and 39-47 as being directed to non-elected subject matter. Withdrawn claims 13-16 remain pending in the application and applicants request rejoinder of these claims with the method of treating cancer claims. In particular, applicants respectfully submit that a technical relationship exists between claims 13-16 and the currently pending claims that involves the same or corresponding special technical feature. Namely, as detailed below, recognition that a compound having the ability to inhibit Rsk activity can be used as an effective anti-neoplastic agent in certain cancers. Accordingly, both sets of claims are directed to the use of specific compounds to inhibit Rsk activity. Therefore, applicants respectfully request that claims 13-16 be rejoined with the currently pending claims for prosecution in the present application.

Applicants acknowledge that the rejection of claims 21-28 and 32 under 35 USC 112, first paragraph has been withdrawn.

Claims 21-28, 32 and 51-53 stand rejected under 35 USC 103 as being obvious over the teachings of Matthes, in view of Eboerbaek, Marks (U.S. 5,910,583), and Kuijpers (U.S.

US App. No. 10/517,328
Response to 12/14/07 Office Action

5,733,523) and Pienta et al (Anticancer Research, 1994, 14, 2617-2620). Applicants respectfully traverse this rejection.

The Examiner has stated in their reasons for maintaining the rejection that the primary Matthes et al reference "teaches that the compound of their [applicants'] invention shows antineoplastic activity". (page 4, last paragraph of the 12/1407 Office Action) Applicants respectfully submit that the Examiner is overstating the teachings of the Matthes reference. In particular, applicants respectfully submit that not all cytotoxic agent are antineoplastic agents. Applicants submit that for a compound to be considered to have antineoplastic activity, the compound must exhibit a physiologically relevant level of cytotoxicity (i.e., most compounds will have a cytotoxic effect if supplied at a high enough concentration). Furthermore, the cytotoxic effect must have some degree of selectivity for cancer cells relative to non-cancer cells (i.e. a compound that kills all cells would not be characterized as having antineoplastic activity). The Matthes reference fails to provide any teaching that would suggest to one of ordinary skill that compound 7 has the requisite properties to be considered an antineoplastic agent.

A close reading of Matthes reveals that the "slightly cytotoxic" compound 7 (data provided in Table 1 and Fig. 1) requires relatively high concentrations of compound 7 (33ug/ml, which is approximately 65 uM) to establish a minor impact on cell viability of a neoplastic rat liver cell line (HTC cells). Applicants submit that this data, showing the compound has very low cytotoxicity against a liver cancer cell line, is insufficient to convince one skilled in the art that the compound has neoplastic activity. Nor would one be motivated to conduct further tests on such a compound when other much more promising compounds have been identified.

Furthermore, Matthes provides no data regarding the cytotoxic effect of compound 7 against non-cancer cells at such a high concentration. We note that at the high dosage of 33

US App. No. 10/517,328
Response to 12/14/07 Office Action

ug/ml, each of compounds 2, 4, 5 and 6 were all found to be toxic to non-cancer 3T3 mouse fibroblasts. Compound 7 was not tested in this assay. Applicants respectfully submit that Matthes likely did not test the cytotoxicity of compound 7 against 3T3 cells because even the Matthes authors did not believe that the compound warranted any further investigation for its potential use as an antineoplastic agent. Perhaps they realized the concentrations of compound 7 they found were necessary to kill cancer cells would also likely kill non-cancer cells.

Contrary to the findings of Matthes, applicants have discovered that "compound 7" does have antineoplastic activity, and at concentrations well below those taught by Matthes as being necessary for cytotoxicity. Unlike Matthes, applicants recognized the antineoplastic effect would be limited to cancer cell lines that are characterized by excessive Rsk activity. The Examiner notes that "the recognition of the mode of action does not lend a patentable distinction". However, applicants respectfully submit that in the present application, recognition of the mode of action allows for the identification of those cancers that the compounds will be effective as an antineoplastic agent. Only by testing the activity of the presently claimed compounds against cancers having excessive Rsk activity are the beneficial properties of the claimed compounds revealed.

Accordingly, while Matthes teach that compound 7 is a poor candidate for an antineoplastic agent, applicants have been able to demonstrate that an inhibitor of Rsk activity will inhibit the growth cancer cells characterized by excessive Rsk activity at physiologically significant concentrations. A "patentable invention may lie in the discovery of the source of the problem even though the remedy may be obvious once the source of the problem is identified." *In re Peehs and Hunner*, 612 f.2d 1287, 204 USPQ 835, 837 (CCPA 1980). Matthes is devoid of any teaching or suggestion that compound 7 could be an effective antineoplastic agent or that the

US App. No. 10/517,328
Response to 12/14/07 Office Action

compound would be effective against a specific class of cancers (i.e., those that have excessive Rsk activity).

Applicants note that the Examiner has made reference to various court decisions regarding the concept of inherency. The Examiner seems to be implying that since the structure of compound 7 was disclosed in Matthes, the use of compound 7 to treat cancer was obvious, as the antineoplastic properties were inherent in the structure of the compound. However, the data provided by Matthes certainly would not lead one to such a conclusion, given the very low and presumably non-specific toxicity of the compound as reported. Furthermore, "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). As noted above, the antineoplastic activity of the claimed compounds is believed to be relevant to cancer cells that are characterized by excessive Rsk activity, and therefore the claimed compounds do not necessarily exhibit antineoplastic activity against any cancer cell, only those that have excessive Rsk activity. Thus, while the antineoplastic activity may be an inherent characteristic of compound 7 itself, the method of using the compounds to take advantage of the previously unknown properties of the compounds to treat a subset of cancers (i.e., those with excessive Rsk activity) was not inherent.

Furthermore, applicants submit "[a]n invitation to investigate is not an inherent disclosure" *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004). This is even more apparent in the present situation

US App. No. 10/517,328
Response to 12/14/07 Office Action

wherein the data presented by Matthes regarding compound 7 does not even rise to the level of an invitation to investigate. There is simply no objective evidence presented by Matthes that would lead on of ordinary skill in the art to believe there would be a reasonable expectation of success of using compound 7 as an antineoplastic agent.

Applicants respectfully submit that they were the first to discover that the claimed compounds have antineoplastic activity against the designated subset of identified cancers. As shown in Example 4, page 36, lines 21-27, SL0101-1 inhibited proliferation of MCF-7 cells but had no effect on the growth of the normal breast cell line, MCF-10A. Applicants have also established that inhibitors of Rsk activity also selectively inhibit the growth of other cancer cell types relative to the corresponding non-cancer types, including ovarian and prostate cancer cells. Applicants have also demonstrated (see Declaration and accompanying data submitted on September 21, 2007) that the Rsk inhibiting compounds can inhibit numerous cancer cell types including for example, cancer cells selected from the group consisting of breast, prostate, leukemia, lung, colon, brain, melanoma, ovarian, and kidney cells at physiologically relevant concentrations (e.g., inhibiting growth by 50% at concentrations less than 25 uM of the active compound). Accordingly, applicants have discovered the surprising result that the claimed compounds have efficacy as antineoplastic agents against a subset of cancer cell types that are characterized by excessive Rsk activity. Matthes simply fails to teach or suggest that their disclosed compound 7 could be used as an effective antineoplastic agent.

Applicants further submit that additional subsequent studies, later published by the National Cancer Institute, further support the conclusion that that compound 7 of Matthes, which is also called 3",4"-O-Deacetylafzelin by Matthes, has no antitumor activity (see Dai et al., 1997, *Natural Product Letters*, 10:115-118; a copy of which was previously submitted with a

US App. No. 10/517,328
Response to 12/14/07 Office Action

Supplementary IDS). The Examiner has discounted the teachings of Dai et al, noting that the inactivity of afzelins is not reported based on the antitumor screen using the same cell lines. However, the objective teaching of that reference cannot be denied, and Dai et al. clearly discourage one from using the present compounds as antineoplastic agents. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Dai et al as well as Matthes simply provided no reasonable expectation that applicants designated compounds would have antineoplastic activity, and yet contrary to these negative teachings applicants investigated and established their neoplastic activity against a subset of cancers.

The data of Dai et al are also published at the National Cancer Institute website for Molecular Targets Development Program, which provides the afzelin structure and indicates that it is a natural product **without** anti-HIV and antitumor activity. That listing also cites Dai. The URL for the NCI website page is <http://home.ncicrf.gov/mtdp/Catalog/compounds/703082.html>, and the relevant compound is labeled as NSC 703082. Applicants again submit that the prior art must be considered in its entirety (i.e., as a whole), including portions that would lead away from the invention in issue. *Panduit Corp. v. Denison Manufacturing Co.*, 810 F.2d 1561 (Fed. Cir. 1987). Therefore, in spite of the Examiner's observation that the compounds of Dai et al were not tested against the same cancers as Matthes, the overall teaching of the prior art, including the primary reference, is that applicants' selected compounds make a poor choice for an antineoplastic agent.

The secondary references fails to counteract the negative teaching of the primary reference or supplement the inadequacies of that teaching with regards to the present invention.

US App. No. 10/517,328
Response to 12/14/07 Office Action

In particular, Bjoerbaek is not even applicable to claims 21-24, 32 and 51-52 because Bjoerbaek fails to provide any disclosure regarding Rsk inhibitors having the structure of applicants' disclosed compounds, nor does that reference disclose any teaching regarding the treatment of cancer. In particular, the Bjoerbaek reference discloses that altering RSK2 activity provides a means for modulating body weight, reducing body fat and reducing sensitivity to diet-induced weight gain. The reference is devoid of any correlation between Rsk activity and cancer. Therefore, prior to applicants' invention there was no reason to believe that Rsk activity was a suitable target for an anti-cancer therapeutic.

The Examiner has cited the secondary references of Kuijpers and Marks as evidence that nucleic acids can be used as anti-neoplastic agents. However, applicants respectfully submit that all nucleic acid based anti-sense and interference RNA therapies are based on the fact that they are designed to specifically interfere with a pre-selected compound that has been associated with a particular disease state. Accordingly, absent the knowledge that Rsk activity can be associated with neoplastic cells, there was simply no reason to attempt to treat cancer using an anti-sense nucleic acid or interference RNA that targets Rsk. The Examiner bears the initial burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden only by showing some objective teaching in the prior art, or that knowledge generally available to one of ordinary skill in the art, would lead the individual to combine the relevant teachings of the references. *In re Fritch*, 972 F.2d 1260 (Fed Cir. 1992).

Here the Examiner has failed to explain why one of ordinary skill in the art would combine the teachings of Bjoerbaek, regarding the use of anti-sense technology to inhibit Rsk activity for the expressed purpose of reducing weight, with the teachings of Kuijpers and Marks, which teach the inhibition of specific cancer associated proteins through the use of anti-sense

US App. No. 10/517,328
Response to 12/14/07 Office Action

technologies. At the time of applicants invention Rsk was not known to be a cancer associated protein and therefore, there is simply no motivation provided by the cited references to target Rsk activity in the context of an anti-neoplastic therapy.

Regarding the other secondary references, the Examiner has failed to describe why the disclosed use of antisense oligonucleotides for inhibiting the expression of the ERBB2 tyrosine kinase receptor oncogene (Marks et al.) as a means of treating cancer would motivate one to use antisense oligonucleotides for inhibiting the activity of Rsk as a means of treating cancer. Furthermore, the Kuijpers reference involves the use of a first nucleic acid sequence that is conjugated to a "targeting agent" and a second nucleic acid sequence that is conjugated to a therapeutically active radioisotope, wherein the first and second nucleic acids are complementary to one another. Again, Kuijpers requires the identification a specific "target" that the targeting agent will bind and allow the second nucleic acid (the "antisense oligonucleotide") to subsequently come in close proximity to the "target" through the binding of the first and second nucleic acids to one another. Prior to applicants' invention Rsk was not known to be a relevant target for treating cancer and therefore there was no motivation for adapting the strategies disclosed in Marks and Kuijpers for targeting Rsk as a means of treating cancer. Therefore, at the time of the invention there was no motivation for combining the teachings of Bjoerbaek with Kuijpers and Marks.

Furthermore, in addition to the lack of motivation to combine the teaching of Bjoerbaek with Kuijpers and Marks, there was simply no reasonable expectation of success associated with inhibiting Rsk activity and providing anti-neoplastic activity. This is because the prior art taken as a whole for all its combined teachings failed to suggest that reducing Rsk activity would reduce a cancer cell's growth.

US App. No. 10/517,328
Response to 12/14/07 Office Action

Lastly, the Examiner has cited Naik et al (Pienta) for its teaching of a compound "structurally very close to the instant compounds" as having anti-cancer activity and thus providing motivation to use the compounds disclosed in the present invention as anti-cancer agents". First of all, applicants respectfully submit the compounds specified in claim 21 are not "structurally very close" to genistein (the compound disclosed in Pienta). Genistein, while including a common bicyclic core relative to the present compounds, is missing an O-linked substituted sugar ring, and has the 4-hydroxy phenyl group at the wrong position of the bicyclic core. Accordingly, the structure of genistein is sufficiently diverse from the presently disclosed compounds that no reasonable expectation could be inferred regarding the sharing of common properties.

Furthermore, applicants note that the structure of the compounds disclosed by Matthes and Dia are much closer in structure than the compounds disclosed in Pienta. However, Matthes and Dia disclose that compounds of the general structure of Formula III are not compounds which exhibit antineoplastic activity. The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). The fact that Matthes and Dia discourage the use of applicants' specific compound SL0101-1 (compound 7) shows there is a substantial degree of unpredictability in the pertinent art area, and one would not have been motivated by a more distant structure (i.e., genistein) to further investigate the compounds of Formula III for their use as antineoplastic agents.

In summary, applicants respectfully submit the Examiner has failed to establish a prima facie case of obviousness. This is due in part to the fact that there is no teaching within any of

US App. No. 10/517,328
Response to 12/14/07 Office Action

the cited references (or any reference made to a generalized teaching known to those skilled in the art) that Rsk activity represented a suitable target for anti-cancer therapies. Without such knowledge, applicants respectfully submit the combination of the Bjoerbaek teachings with Kuijpers and Marks is not proper, because antisense therapies are based on the identification of a specific target. Absent knowledge of the involvement of Rsk in cancer cells, there was no reason to attempt an anticancer therapy that utilized antisense induced inhibition of Rsk.

Furthermore, while the prior art reference of Matthes disclosed one of applicants' specific compounds, and actually tested the compound for its cytotoxicity, the reference failed to appreciate the utility of that compound for a subset of cancer types (i.e., those having an excess of Rsk activity). Accordingly, the references (i.e., both Matthes and Dai) that specifically disclosed one of applicants' disclosed compounds discourage their use as neoplastic agents due to their low cytotoxicity. The failure to recognize the utility of the claimed compounds is believed to derive directly from the fact that the prior art failed to appreciate that the antineoplastic activity is limited only to a subset of cancer types. Accordingly, it is only through applicants' discovery that inhibiting Rsk activity can be used as a mechanism to treat a certain subset of cancers that lead to the present method of treating cancer.

Claims 21-28, 32 and 51-53 are believed to be patentable over the combined teachings of Matthes, Bjoerbaek, Marks, Kuijpers (U.S. 5,733,523) and Pienta et al., and applicants respectfully request the withdrawal of the rejection of claims 21-28, 32 and 51-53 over those references.

The foregoing claim amendments and remarks are believed to fully respond to the Examiner's rejections and the claims are believed to be in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance. If any

US App. No. 10/517,328
Response to 12/14/07 Office Action

further discussion of this matter would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,



John P. Breen
Registration No. 38,833
Attorney for Applicants

(317) 261-7940
Indianapolis, Indiana 46204